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Glu-155 and one or more residues selected from the group  
consisting of Ala-14, Gly-29, and Ala-46 of the amino acid  
sequence aligned with SEQ ID NO:7.

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REMARKS

The official action of October 4, 1999, and the prior art cited and relied upon therein have been carefully reviewed. The claims under consideration in the present application (not including the non-elected claims) are now claims 1-4 and 23, and these claims define patentable subject matter warranting their allowance. Favorable reconsideration and allowance are respectfully urged.

Applicants' specification has been criticized as being replete with grammatical and idiomatic errors too numerous to mention specifically. While applicants respectfully disagree, on the other hand applicants hereby express their willingness to cooperate fully in this regard. Accordingly, if the examiner notices any portions of the specification which she feels should be revised, applicants request that these be brought to their attention.

As regards those specific criticisms appearing at the bottom of numbered page 2 of the official action, these have been addressed above.

As regards the heading appearing near the top of page 4, it is respectfully noted that headings are not required, let alone their specific content. In other words, the guidelines are suggestive and not mandatory, and therefore the PTO cannot "require" an applicant to use any headings, let alone any specific form of heading. Nevertheless, in deference to the examiner's views, the heading near the top of page 4 has been amended.

As regards the trademarks at the bottom of pages 2 and 30, it is to be noted that some trademarks take a stylized form; and one common stylized form, evident in both trademarks in question, is to have a single word wherein some of the letters are capitalized and some are not. It is believed that the form of the two trademarks in question is correct as set forth in the original text of applicants' specification, and therefore any change would be improper. Nevertheless, if the examiner insists, applicants would be willing to fully capitalize both trademarks, even though this would deviate from the forms in which these trademarks are actually believed to appear.

Claims 1-6 have been rejected under §101 as directed to non-statutory subject matter. Claim 6 has been rejected under the first paragraph of §112. Claims 1-6 have been rejected under the second paragraph of §112. These rejections

are respectfully traversed, especially insofar as they might presently be deemed to apply.

Claims 5 and 6 have been deleted, and therefore the rejections are moot at the present time insofar as they relate to claims 5 and 6. Claim 1 has been amended to call for a purified human Desert hedgehog protein comprising the amino acid sequence of SEQ ID NO:1. Claims 2-4 have been amended to delete the expression "contains a part or the whole of". Support for these amendments will be found in the specification as filed, for example at page 5, lines 3-8; page 24, lines 6-16; and page 33, lines 12-24.

The above amendments are believed to obviate or moot the aforementioned rejections under §§101 and 112. Such amendments have been made to better particularly point out and distinctly claim the invention.

New claim 23 has been added above, directed to a purified human Desert hedgehog protein obtainable by expression of a DNA from human cell, wherein the DNA comprises a nucleotide sequence at least 90% identical with SEQ ID NO:7 and encodes a contiguous amino acid sequence which conserves amino acid residues corresponding to Glu-155 and one or more residues selected from the group consisting of Ala-14, Gly-29, and Ala-46 of the amino acid sequence aligned with SEQ ID NO:7.

Support for the new claim 23 will be found in the specification as filed, e.g. in the specification from page 23, fifth line from the bottom, to page 24, line 16, where it is disclosed that isolated DNA of SEQ ID NO:7 which encodes human Desert hedgehog protein exhibited a significant homology of about 89% to the nucleotide sequence of a mouse Desert Hedgehog gene. Since it is well known that the closer the species become, the higher the homology generally observed in DNAs which encode equivalent proteins in different species, the disclosure at pages 23 and 24 indicates that human Desert hedgehog protein is an expression of DNA which comprises a nucleotide sequence at least 90% identical with SEQ ID NO:7.

On the other hand, as shown in the attached Reference Figure 1, the amino acid sequence of the human Desert hedgehog protein of SEQ ID NO:1 is different from other related proteins at Ala-14, Gly-29, Ala-46 and Glu-155, while relatively high homology is observed in other regions. This means that the amino acid sequence of the human Desert hedgehog protein is characterized by one or more amino acid residues selected from the group consisting of Ala-14, Gly-29, and Ala-46 of the amino acid sequence aligned with SEQ ID NO:7 and by Glu-155. It is believed that new claim 23 is well supported by the specification and is novel and non-obvious from any known prior art.

Claims 1-5 have been rejected as obvious under §103 from Tate et al ("Tate") in view of Kormsmeier USP 5,955,595 ("Kormsmeier") and Ingham et al USP 5,844,079 ("Ingham"). This rejection is respectfully traversed.

The rejection states that Tate teaches the complete encoded amino acid sequence of a human desert hedgehog protein and part of the encoding DNA sequence. However, the examiner's attention is respectfully invited to the fact that Tate "GenBank Accession Number AB010994" was published February 14, 1998, while the present application has a first priority date of April 25, 1997. Accordingly, Tate is not "prior art" and cannot be relied upon. To support applicants' allegation in this regard, attached hereto please find a verified English translation of applicants' Japanese priority application 121578/1997, filed on April 25, 1997. As Tate is not "prior art", the rejection must therefore fall.

It should be briefly added that even if Tate were available as prior art, the amino acid sequence disclosed in Tate does not coincide exactly with SEQ ID NO:1 of the present invention, as is apparently recognized by the PTO. The rejection continues, stating that Ingham teaches mouse Desert hedgehog, mouse and human Indian hedgehog, and mouse, chicken, human and zebrafish Sonic hedgehog. However, Ingham does not

teach human Desert hedgehog protein. Important differences are shown in the attached Reference Figure 1.

Accordingly, even if Tate were available as prior art, which it is not, no combination obvious to those of ordinary skill in the art would result in applicants' claimed subject matter. Withdrawal of the rejection is in order and is respectfully requested.

Claims 1-5 have also been rejected as obvious under §103 from Drummond in view of Ingham. This rejection is also respectfully traversed.

The rejection states that Drummond teaches part of the nucleic acid encoding human Desert hedgehog protein and that it would have been obvious to obtain the full-length coding region of the human Desert hedgehog nucleic acid of Drummond using one of the methods of Ingham. It is said that Ingham teaches mouse Desert hedgehog, mouse and human Indian hedgehog, and mouse, chicken, human and zebrafish Sonic hedgehog. However, as noted above, Ingham never teaches human Desert hedgehog protein.

In contrast to the prior art, the claimed invention is directed to a purified human Desert hedgehog protein comprising the amino acid sequence of SEQ ID NO:1. Again, Reference Figure 1, prepared by applicants, shows the differences between the amino acid sequence of SEQ ID NO:1 of

the present invention (see line A), Drummond's partial sequence (see line B), the mouse Desert hedgehog protein of Ingham (see line C) and the human Sonic hedgehog protein of Ingham (see line D).

As is quite clear from Reference Figure 1, the amino acid sequence of SEQ ID NO:1 is not identical to any of the other sequences. Even Drummond's partial sequence (see line B) is different from SEQ ID NO:1 at the position of 155 "Glu". Furthermore, the amino acid sequence of SEQ ID NO:1 is different from any of the other sequences at the positions of 14 "Ala", 29 "Gly" and 46 "Ala".

While, as the examiner indicates in the official action, one may have been motivated to perform cross-species comparisons with Desert hedgehog protein for other related proteins of Ingham, it would not have been expected that the amino acid residues at positions 14, 29, 46 and 155 of the human Desert hedgehog protein would be "Ala", "Gly", "Ala" and "Glu", respectively. There would have been no reasonable expectation of reaching the amino acid sequence of SEQ ID NO:1 of the present invention based on the disclosures of Drummond and Ingham, even if it would have been obvious to attempt to combine these.

Withdrawal of the rejection is in order and is respectfully requested.

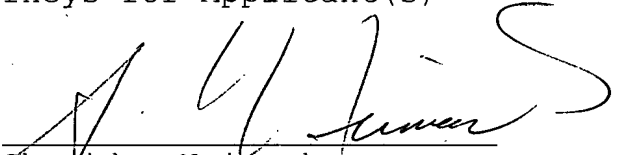
The prior art documents made of record and not relied upon have been noted, along with the implication that such documents are deemed by the PTO to be not sufficiently pertinent to warrant their application against any of applicants' claims.

Favorable reconsideration and allowance are respectfully urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.  
Attorneys for Applicant(s)

By

  
Sheridan Neimark  
Registration No. 20,520

SN:rd

Telephone No.: (202) 628-5197

Facsimile No.: (202) 737-3528

itt3\sn\ariyasul.amd.doc